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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
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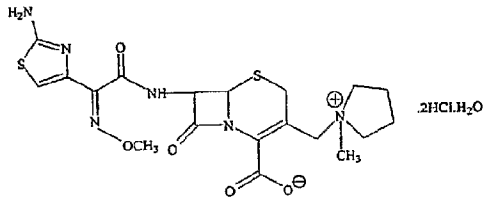
(54) **Title:** A NOVEL INTERMEDIATE FOR THE PREPARATION OF CEFEPIME



(I)

(57) **Abstract:** A novel process is disclosed for preparation of cefepime, a cephalosporin antibiotic in two steps comprising of (i) acylation of 7-Amino-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate hydrochloride (IV) with 4-bromo-2-methoxyimino-3-oxobutyric acid chloride (III) to give 7-(4-bromo-2-methoxyimino-3-oxobutyramido)-3--[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate (II), (ii) cyclisation of bromo compound II with thiourea to give cefepime (I) and (iii) purification of cefepime.

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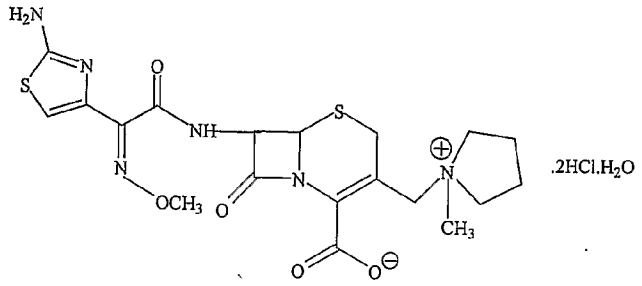
A NOVEL INTERMEDIATE FOR THE PREPARATION OF CEFEPIME

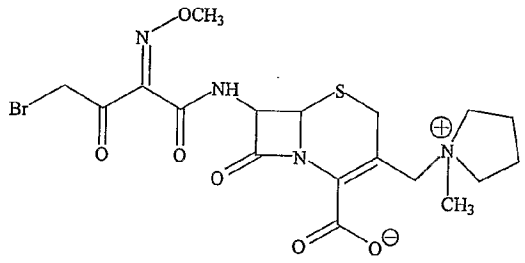
FIELD OF INVENTION

The present invention is related to provide a novel process for preparation of cefepime of formula I, a cephalosporin antibiotic.



I

The present invention further relates to provide a process for preparation of a novel intermediate of formula II which is useful for the preparation of Cefepime of formula I.



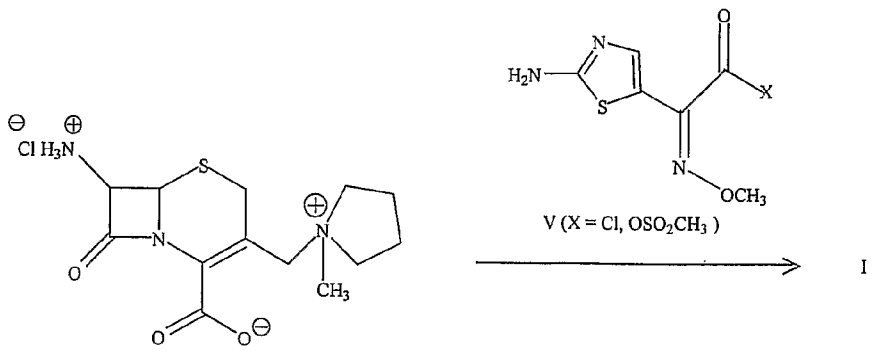
II

BACKGROUND OF THE INVENTION

A large number of cephalosporin antibiotics are known and are widely used in the treatment of bacterial infection. The semi-synthetic antibiotic cefepime is a useful broad-spectrum antibiotic which was first described by Aburaki, et al, in U.S. Pat. No. 4,406,899 wherein the cefepime was synthesized by a multistep process involving protection and deprotection steps thereby making the process lengthy and laborious.

The patents US 4,754,031; US 5,594,129 and 5,594,130 disclose synthesis of cefepime as shown below which involves acylation of 7-amino-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate hydrochloride (IV) with 2-(2-amino-4-thiazolyl)-2-methoxyiminoacetic acid that is activated by converting to chloride by

reacting with chlorinating agent such as thionyl chloride or phosphorous pentachloride or to anhydride by reacting with methane sulphonyl chloride.



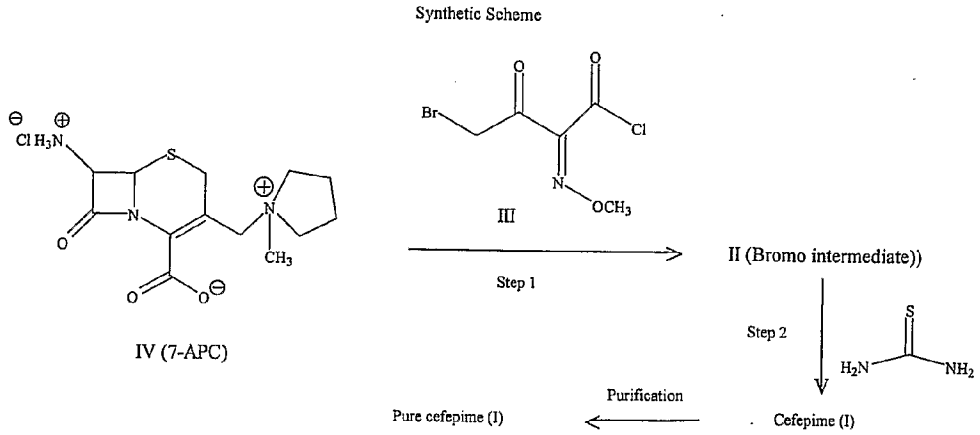
IV (7-APC)

OBJECTIVES OF THE INVENTION

The objective of the present invention is to provide a novel process for preparation of cefepime (I) comprising of (i) acylation of 7-Amino-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate (7-APC, IV) obtained in step 1 with 4-bromo-2-methoxyimino-3-oxobutyric acid chloride (III) to give provide 7-(4-bromo-2-methoxyimino-3-oxobutyramido)-3--[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate (bromo intermediate, II), (ii) cyclisation of bromo compound (II) with thiourea to give cefepime (I) and (iii) purification of cefepime.

DETAILED DESCRIPTION

The present invention provides a novel process for the preparation of cefepime of formula (I) as shown in synthetic scheme below.



The starting material 7-Amino-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate (7-APC, IV) was prepared as per process described in patent US 5,594,131 by reaction of disilylated 7-amino-3-acetoxymethyl-ceph-3-em-4-carboxylate with N-methyl pyrrolidine in cyclohexane. The compound 7-APC was isolated as anhydrous or in the form of acid addition salts of HCl, HBr, HI and H_2SO_4 or hydrates of these salts.

In an embodiment of the present invention, the preparation of compound of formula II involves condensation of 4-bromo-3-oxo-2-methoxyimino-butyryl chloride of formula III with 7-amino-3-[(1- methyl1-pyrolidino) methyl] ceph-3-em-4-carboxylate hydrochloride of formula IV to provide 7-(4-bromo-2-methoxyimino-3-oxobutyramido)-3--[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate (bromo intermediate, II) as shown in step 1. The starting compound 7-APC (IV) in the step 1 is used as mono-addition salt or as a di-addition salt with HCL, HBr, HI, H_2SO_4 and H_3PO_4. These addition salts may additionally be present in solvated form, e. g. as monohydrate or dihydrate, most preferably mono hydrochloride salt of 7-APC is used.

The another starting material of condensation reaction is 4-bromo-2-methoxyimino-3-oxo-butyric acid chloride (III) is prepared from reaction of ammonium salt of 4-bromo-2-methoxyimino-3-oxo-butyric acid with chlorinating agent such as phosphorous pentachloride, phosphorous oxychloride, oxalyl chloride and thionyl chloride halogenated solvent such as dichloromethane or ethylene dichloride.

The solvent for condensation reaction is selected from dichloromethane, ethylene dichloride, ethyl acetate, methanol, ethanol, propanol, butanol, acetone, ethyl methyl ketone, acetonitrile, diisopropyl ether, tetrahydrofuran, dioxane, dimethyl formamide, water and mixtures thereof. The ratio of organic solvent to water in the mixture is in the range of 10:90 to 90:10, more preferably 50:50. The pH is maintained at 5.0-7.0, preferably at 5.4-6.0 by using organic or inorganic base selected from triethyl amine, pyridine, sodium hydroxide, sodium hydrogen carbonate, sodium carbonate, potassium hydroxide, potassium hydrogen carbonate, potassium carbonate, ammonia and ammonium carbonate, more preferably potassium hydrogen carbonate. The reaction is performed at temperature-20 to 30°C, preferably at –10 to –15°C.

In another embodiment of the present invention the compounds of formula II may be isolated in the form free base or as acid addition salts of HCl, HBr, HI and H_2SO_4 or hydrates of these salts.

In yet another embodiment of the present invention the compound of formula II is treated with thiourea to undergo cyclisation reaction to give cefepime as shown in step 2. The solvent used for cyclisation reaction is selected from dichloromethane, ethylene dichloride, ethyl acetate, methanol, ethanol, propanol, butanol, acetone, ethyl methyl ketone, acetonitrile, diisopropyl ether, tetrahydrofuran, dioxane, dimethyl formamide, water and mixtures thereof. The ratio of organic solvent to water in the mixture is in the range of 10:90 to 90:10, more preferably 50:50. The pH is maintained at 3.5-5.5, preferably at 4.0-4.5 by using organic or inorganic base selected from triethyl amine, pyridine, sodium hydroxide, sodium hydrogen carbonate, sodium carbonate, potassium hydroxide, potassium hydrogen carbonate, potassium carbonate, ammonia and ammonium carbonate, more preferably potassium hydrogen carbonate. The reaction is performed at temperature 10 to 50°C, preferably at 25 to 30°C.

In yet another embodiment of the present invention the cefepime is purified by dissolving in alcoholic solvent such as methanol, subjected to carbon treatment, filtering and crystallizing out pure cefepime by addition of ketonic a solvent such as acetone. The purification is performed at temperature 10 to 50°C, preferably at 25 to 30°C.

The cefepime dihydrochloride monohydrate (I) thus obtained is highly pure (HPLC purity ≥ 99.7%) and stable.

The present invention has following advantages:

(i) the process provides highly pure and stable cefepime dihydrochloride monohydrate in good yield,

(ii) the process utilizes avoids the use of silylated reagents in step 1, thereby it reduces the load of effluents. Thus, the process of the present invention is operationally simple and more eco friendly.

(iii) the process is commercially viable as there are no protection and deprotection steps involved.

The present invention is illustrated in the following examples without limiting the scope of the invention.

Example 1

Step 1 7-[4-Bromo-2(Z)-methoxyimino-3-oxobutyramide]- 3-[(1- methyl -1-pyrolidino) methyl] ceph-3-em-4-carboxylate hydrochloride (II)

A mixture of phosphorous pentachloride (74.5 g, 0.3573 mol.), dichloromethane (500ml) was cooled to –10°C. Ammonium salt of 4-bromo-2-oxyimino-3-oxo butyric acid was added in lots at –10 to-15°C. Mixture was stirred at 30°C for 30 min. and 0 to 5°C for 30 min. Dichloromethane was evaporated completely. To this acetone (250 ml) was added. In another flask the mixture of acetone (500 ml), water (500 ml) and 7-amino-3-[(1-methyl1-pyrolidino) methyl] ceph-3-em-4-carboxylate hydrochloride (100g) was cooled to –10°C. pH was adjusted to 6.5 by 25% potassium bicarbonate solution. Acid chloride was added slowly by maintaining pH 5.4 to 5.8 at –5 to –10°C. Mixture was stirred for 20 minute. pH was adjusted to 0.7 slowly by concentrated hydrochloric acid at 0 to –5°C. Mixture was stirred for 2 hr at same temperature, filtered washed with (1:1) acetone-water (400ml) and acetone (400ml). Drying under vacuum at 40°C affords 7-[4-Bromo-

2(Z)-methoxyimino-3-oxobutyramide]- 3-[(1- methyl -1-pyrolidino) methyl] ceph-3-em-4-carboxylate hydrochloride (bromo intermediate, II) (120g, 74.4%).

Purification of bromo intermediate (II)

The mixture of acetone (500 ml), water (500 ml) and 7-[4-Bromo-2(Z)-methoxyimino-3-oxobutyramide]- 3-[(1- methyl -1-pyrolidino) methyl] ceph-3-em-4-carboxylate hydrochloride (100g) obtained above was cooled to –10°C. The pH of the mixture was adjusted to 4 to dissolve completely by 25% potassium bicarbonate. Carbon (10 g) was added and mixture was stirred for 30 minutes at 0 to 5°C. Filtered and the pH of filtrate was adjusted by dilute hydrochloric acid to 0.7. Slurry was stirred for 2 hr at 0 to-5°C, filtered washed with water and acetone, drying under vacuum at 40°C affords (85g) pure 7-[4-bromo-2(Z)-methoxyimino-3-oxobutyramide]- 3-[(1- methyl -1-pyrolidino) methyl] ceph-3-em-4-carboxylate hydrochloride (85g)

Step 2

Preparation of 7-[2-(2-aminotiazol-4yl)-2-(z)-methoxy-iminoacetamido]-3-[(1-methyl-1-pyrolidino)-methyl] ceph-3-em-4carboxylate dihydrochloride monohydrate (cefepime, I).

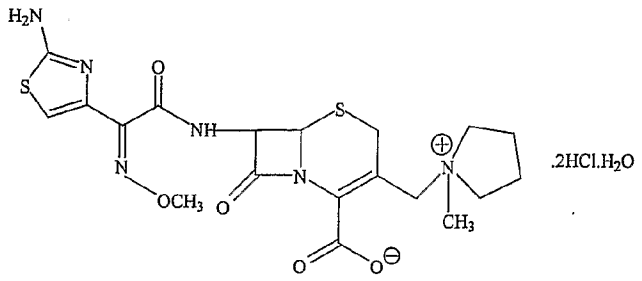
A mixture of 7-[4-bromo-2(Z)-methoxyimino-3-oxobutyramide]- 3-[(1- methyl -1-pyrolidino) methyl] ceph-3-em-4-carboxylate hydrochloride (II) (80g, 0.1481mol), acetone (400ml), water (400ml) was cooled to 10°C. pH of mixture was adjusted to 4 by 25% potassium bicarbonate , thiourea (15.68g, 0.2063 mol) was added. Mixture was stirred for 90 min at pH 4.2 to4.5 at 25°C. Carbon (12 g) was added and stirred for 1 hr, filtered washed with water (80ml). pH of filtrate was adjusted to 0.5 by concentrated hydrochloric acid at 8-10°C. Acetone (3440ml) was added slowly in 2 hr at 8-10°C. After stirring for 1 hr at 8-10°C mixture was filtered, washed with acetone (400 ml) gives cefepime dihydrochloride monohydrate 88 g (94.5% yield, purity 99.3%).

Purification of cefepime dihydrochloride monohydrate:

Cefepime (80) g obtained above was dissolved in DM water (400 ml) under stirring. To that acetone (1200 ml) was added slowly in 30 min at 25-28°C. Mixture was stirred for 30 min at same temp. Acetone (2000 ml) was added slowly in 1hr at 25-28°C. Mixture was stirred for 1hr, filtered and washed with acetone (400ml), dried under vacuum at 40°C gives pure cefepime dihydrochloride monohydrate 75 g (93% yield, purity 99.7%).

CLAIMS

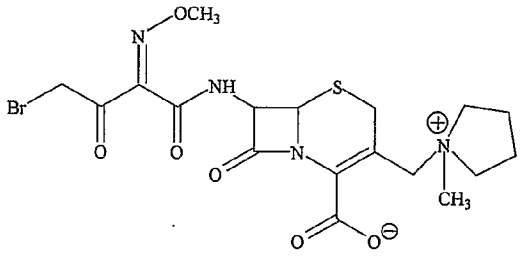
1. A process for preparation of cefepime of formula (I)



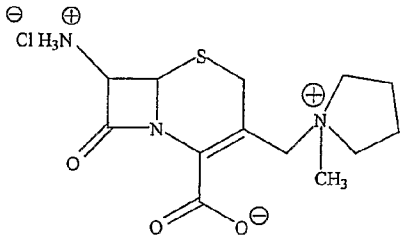
I

comprising the steps:

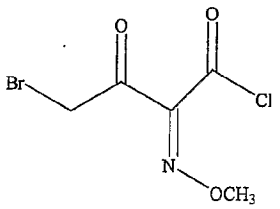
(i) acylation of 7-Amino-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate (7-APC, IV) with 4-bromo-2-methoxyimino-3-oxobutyric acid chloride (III) to give provide 7-(4-bromo-2-methoxyimino-3-oxobutyramido)-3--[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate (bromo intermediate, II)



II



IV



III

(ii) cyclisation of bromo compound (II) with thiourea to give cefepime (I) and

(iii) purification of cefepime.

2. A process as per claim 1 wherein, the step 1 is carried out in solvent selected from dichloromethane, ethylene dichloride, ethyl acetate, methanol, ethanol, propanol, butanol, acetone, ethyl methyl ketone, acetonitrile, diisopropyl ether, tetrahydrofuran, dioxane, dimethyl formamide, water and mixtures thereof, preferably mixture of acetone and water.

3. A process as per claim 2 wherein, the ratio of acetone and water in the step 1 is in the range of 10:90 to 90:10, more preferably 50:50.

4. A process as per claim 1 wherein, step 1 is carried out at pH 5.0-7.0, preferably at 5.4-6.0.

5. A process as per claim 1 wherein, the pH 5.4-6.0 in step 1 is maintained by using organic or inorganic base selected from triethyl amine, pyridine, sodium hydroxide, sodium hydrogen carbonate, sodium carbonate, potassium

hydroxide, potassium hydrogen carbonate, potassium carbonate, ammonia and ammonium carbonate, most preferably potassium hydrogen carbonate.

6. A process as per claim 1 wherein, the step 1 is performed at temperature-20 to 30°C, preferably at –10 to –15°C.

7. A process as per claim 1 wherein, the step 2 is carried out in solvent selected from dichloromethane, ethylene dichloride, ethyl acetate, methanol, ethanol, propanol, butanol, acetone, ethyl methyl ketone, acetonitrile, diisopropyl ether, tetrahydrofuran, dioxane, dimethyl formamide, water and mixtures thereof, preferably mixture of acetone and water.

8. A process as per claim 2 wherein, the ratio of acetone and water in the step 2 is in the range of 10:90 to 90:10, more preferably 50:50.

9. A process as per claim 1 wherein, step 2 is carried out at pH 3.3 to 5.5, preferably at 4.0 to 4.5.

10. A process as per claim 1 wherein, the pH in step 2 is maintained by using organic or inorganic base selected from triethyl amine, pyridine, sodium hydroxide, sodium hydrogen carbonate, sodium carbonate, potassium hydroxide, potassium hydrogen carbonate, potassium carbonate, ammonia and ammonium carbonate, most preferably potassium hydrogen carbonate.

11. A process as per claim 1 wherein, the step 1 is performed at temperature 10-50°C, preferably at 25-30°C.

12. A process as per claim 1 wherein, the step 3 is carried out by dissolving cefepime in alcoholic solvent such as methanol and crystallizing out pure cefepime by addition of ketonic a solvent such as acetone.

13. A process as per claim 1 wherein, the step 3 is performed at temperature 10 to 50°C, preferably at 25 to 30°C.

5

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2005/000406

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D501/00 C07D501/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/092183 A (SANDOZ AG; LUDESCHER, JOHANNES; STURM, HUBERT; WOLF, SIEGFRIED) 28 October 2004 (2004-10-28) claim 1; example 5	1-13
Y	EP 0 324 418 A (TAKEDA CHEMICAL INDUSTRIES, LTD) 19 July 1989 (1989-07-19) p.4, compounds (VIII), (IX), (X) ans (XI), steps 6 and 7; working example 4, step (4); claim 2	1-13
Y	WO 02/083634 A (RANBAXY LABORATORIES LIMITED; KUMAR, YATENDRA; TEWARI, NEERA; ARYAN, R) 24 October 2002 (2002-10-24) claims 1,3,4	1-13

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
11 April 2006	09/05/2006

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2005/000406

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/019227 A (ORCHID CHEMICALS & PHARMACEUTICALS LTD; PANDURANG, BALWANT, DESHPANDE;) 3 March 2005 (2005-03-03) the whole document	1-13
P,X	US 2005/043531 A1 (HANDA VIJAY KUMAR ET AL) 24 February 2005 (2005-02-24) claims 1,2,5,7	1-13

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2005/000406

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004092183 A	28-10-2004	EP 1618114 A2	25-01-2006
EP 0324418 A	19-07-1989	CN 1035283 A	06-09-1989
		CN 1124737 A	19-06-1996
		HU 49884 A2	28-11-1989
		JP 1230547 A	14-09-1989
		US 5109131 A	28-04-1992
WO 02083634 A	24-10-2002	BR 0208999 A	22-03-2005
		CN 1520418 A	11-08-2004
		EP 1389187 A2	18-02-2004
		JP 2005511480 T	28-04-2005
		US 2005020561 A1	27-01-2005
WO 2005019227 A	03-03-2005	US 2006058281 A1	16-03-2006
		US 2005080070 A1	14-04-2005
US 2005043531 A1	24-02-2005	NONE	